REMARKS

A. Status of the Claims

Claims 24-34 were pending at the time of the Action, with claims 24-32 being withdrawn from consideration. Claims 24-32 have been canceled. Applicant reserves the right to pursue the subject matter of the canceled claims in one or more divisional patent applications. Claim 33 has been amended and new claims 35-42 have been added. No new matter was added by these amendments.

B. Restriction Requirement

Although the Examiner has made final the restriction requirement between the Group I and Group II inventions, Applicants object to the inaccurate characterization of the teachings of the specification presented on pages 2 and 3 of the Office Action dated September 8, 2008. In particular, the Examiner stated that the Novak Declaration, which explains that type I tau molecules are conformationally distinct from the tau molecule described in WO 96/30766, was ineffective because the specification did not set forth this distinction. This is incorrect. As explained in Applicants previous response, the tau molecule described in WO 96/30766 corresponds to the tau core fragment disclosed by Novak *et al.* (1993) (IDS ref. C8), which is discussed on page 4 of the present specification. Further studies of this tau core fragment were described by Fasulo et al. (1996), which is also discussed on page 4 of the present specification. The specification states that the tau polypeptides described by Novak *et al.* (1993) "do not have biological structural pathological properties common with 'real world' tau proteins, especially tau proteins being connected with Alzheimer's disease." Specification, p. 4. Thus, the Novak Declaration provides additional evidence of a distinction that was ***already*** set forth in the specification.

C. Claim Rejections Under 35 U.S.C. § 112

The Action rejected claims 33-34 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Action acknowledged that the specification is enabling for making a transgenic mouse comprising a genome having a double truncated tau sequence integrated therein, but argued that the specification does not reasonably enable making a transgenic animal of any species, wherein the genome of the animal comprises a double truncated tau sequence integrated into the endogenous tau equivalent gene and further wherein the animal exhibits Alzheimer's disease associated risk factors. Applicant traverses this rejection.

Applicant incorporates by reference the arguments in the response filed on June 9, 2008. These arguments established that the current claims are enabled by the specification. The Examiner's response to these arguments are deficient for a number of reasons. First, in paragraph 8 of the Action, the Examiner argues that because the phenotypes of the different rat lines described in the Filipcik Declaration are different in strength, this is evidence of the unpredictability of generating transgenic animals. It is clear, however, from the Filipcik Declaration that the strength of the phenotype is not an issue because ***all*** rat lines produced had the tauopathic phenotype. Thus, the generation of transgenic animals with relevant phenotypes was not unpredictable.

Moreover, it is known by those of ordinary skill in the art that strength of phenotype generally depends on gene dosage of the transgene. This means that transgenic animals with a higher gene dosage of, for example, tau type IIA molecules will show a stronger phenotype compared to animals with a lower gene dosage of tau type IIA molecules. The relationship between gene dosage and strength of phenotype is documented in the scientific literature (see SantaCruz et al., IDS ref. C35). Accordingly, the strength of the tauopathic phenotype is predictable based on gene dosage, which can be quantified even before the phenotype of the

transgenic animal appears. As mentioned above, however, ***all*** rat lines described in the Filipcik declaration had the tauopathic phenotype.

Dr. Filipcik is a co-author of a recent publication, Koson *et al.*, *European Journal of Neuroscience*, 28:239-246 (2008), IDS ref. C31), which describes studies on the expression levels of truncated human tau protein in transgenic rats. The transgenic rat lines described in the Koson publication were generated in the SHR72 and SHR318 lines, and both lines were hemizygous for the truncated human tau protein. The truncated human tau protein was expressed at an approximately 44% higher level in the SHR72 line than in the SHR318 line. As shown in Figure 1 of Koson, both transgenic rat lines displayed significantly shorter life spans as compared to control rats. In addition, the magnitude of this effect was related to the level of truncated tau expression, with the SHR72 having a shorter life span that SHR318. These data, therefore, confirm that the strength of phenotype in these transgenic rats is predictable and gene dose dependent.

The Examiner also continues to assert that the specification should teach which specific amino acids are substituted, deleted or inserted within the minimally truncated tau core (Action, p. 7). The claims refer to N- and C-terminally double truncated type IA tau molecule, type IB tau molecule, type IIA tau molecule, or type IIB tau molecules. There is no recitation in the claims of amino acids that are substituted, deleted or inserted within the minimally truncated tau core. Thus, the Examiner's argument in this regard is without merit and should be withdrawn.

The examiner also argues that the specification does not adequately disclose the specific promoters that should be used to achieve transgene expression (Action, p. 8-9). Enablement must be evaluated from the position of a person of ordinary skill in the art. Moreover, "a patent need not teach, and preferably omits, what is well known in the art." *Hybridtech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1987). The Examiner admits that it was

well known at the time of filing that expression of a gene of interest in a transgenic animal requires operable linkage of the gene to a promoter (Action, p. 8), and that it was also well know in the art that not all promoters result in efficient expression in the appropriate target tissue (Action, p. 8). Given that the Examiner finds that such things were so well known, why wouldn't a person of ordinary skill in the art be able to make and use them?

The Examiner's argument that expression of a gene of interest in a transgenic animal requires operable linkage of the gene to a promoter is further unavailing because the claims do not recite a promoter and do not need to. Expression of a gene of interest in a transgenic animal requires many well-known things including, for example, numerous components for transcription and translation of the gene. Patent claims set forth the limitations of a claimed invention. It is not the purpose of patent claims to describe all of these other elements.

The Examiner's argument that not all promoters result in efficient expression in the appropriate target tissue is also unavailing. Numerous promoters were known and readily available to those in the art at the time of the filing of the present application. Examples of some promoters that have been used to drive transgene expression in the central nervous system of various mammals are provided in the review article by *Fitzsimons et al* (IDS ref. C24); *see e.g.,* Tables 1 and 2). The cytomegalovirus (CMV) promoter, for example, had been used to drive the expression of several different transgenes in the central nervous system of rat, mice, and monkeys (Fitzsimons, Table 1). In addition, the publication by Lewis *et al.* (IDS ref. C32) shows the expression of human tau protein in mice using the mouse prior promoter (MoPrP). *See also* Andrae *et al.* (IDS ref. C16); Ikenaka *et al.* (IDS ref. C30); Quinn (IDS ref. C33); Glorioso *et al.* (IDS ref. C25); and Bornemann *et al.* (IDS ref. C18).

Furthermore, generation of transgenic animals was at the time of patent application filing a standard procedure described in a number of publications (see Araki *et al.* (IDS ref. C17);

Hammer *et al.* (IDS ref. C27); Brinster *et al.* (IDS ref. C20); Charreau *et al.* (IDS ref. C23); Campbell *et al.* (IDS ref. C21); Si-Hoe *et al.* (IDS ref. C36); Richa *et al.* (IDS ref. C34). In addition to the rats described in the Filipcik Declaration, a variety of other animal models would be suitable models since relevant pathology occurs in a number of animals. For example, Hartig *et al.* (IDS ref. C28) shows that PHF-like tau occurs in hamsters, which parallels the situation in AD (abstract). Hartig also notes that PHF-like tau was observed in ground squirrels (p. 69, right col., para. 2).

Huang *et al.*, (IDS ref. C29) describes neurofibrillary tangles based on abnormal tau in rabbits. The proteins have a molecular structure that closely resembles that of primates, thus making such an animal system of relevance for human neurodegenerative disease like AD (abstract, p. 214, left col., para. 2, p. 219, left col., para. 2).

Gotz (IDS ref. C26) describes the use of murine models expressing tau as system for the dysfunction of tau and neurodegeneration and dementia based on neurofibrillary lesions (abstract, p. 275, right col., item 4.3). In addition, Lewis *et al.*, (IDS ref. C32) describes the formation of AD related NF tangles through expression of mutant human tau in mice (abstract). These reference demonstrate that a variety of animals are capable of exhibiting tauopathic phenotypes.

In view of the fact that (a) the present specification provides sequences of N- and C-terminally double truncated type IA tau molecule, type IB tau molecule, type IIA tau molecule, or type IIB tau molecules; (b) promoters capable of driving expression in neurons were known in the art at the time of filing; and (c) technologies for generating transgenic animals were described in the specification (*e.g.*, Example 14) and known in the art at the time of filing; a person of ordinary skill in the art could have made and used the claimed invention without undue experimentation.

In view of the above, the claims are enabled. Applicant, therefore, requests the withdrawal of this rejection.

D. Double Patenting

Claims 33-34 were provisionally rejected for nonstatutory obviousness-type double patenting over claims 17-21 of copending Application No. 10/521,049. A provisional double-patenting rejection, however, is not a final rejection that blocks the prosecution of all of the conflicting applications. If a provisional double-patenting rejection is the only rejection remaining in an application, the Examiner should withdraw the rejection and permit the application to issue as a patent. MPEP § 804(I)(B). After one application issues as a patent, the provisional double-patenting rejection in the remaining application is converted to an actual double patenting rejection. Id. Thus, either the present application or the '049 application must issue as a patent before an actual double patenting rejection may be raised against the remaining application. Applicant will file a terminal disclaimer, if appropriate, at that time.

E. Conclusion

Applicant believes that these remarks fully respond to all outstanding matters for this application. Applicant respectfully requests that the rejections of all claims be withdrawn.

Respectfully submitted,

Travis M. Wohlers
Reg. No. 57,423
Attorney for Applicant

(Customer No. 32425)
FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
512.536.5654 (Voice)
512.536.4598 (Fax)

Date: January 8, 2009